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Review of randomized controlled trials of nutritional supplementation in people living with HIV

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Background: Nutritional deficiencies are widespread in people living with HIV (PLWH), prior to the antiretroviral treatment (ART). Nutrient deficiencies and other nutrition-related conditions, however, have been identified in patients receiving ART. Trials of nutritional supplementation have been conducted to alleviate these nutritional conditions and improve or reverse nutrition-related outcomes. This review aims to evaluate the benefits of supplementation, its unintended adverse effects, and the difference in approach and focus, research design, formulations, and outcomes between those randomized clinical trials (RCTs) conducted before and after the initiation of ART.

Methods: An evidence-based systematic review of the literature was conducted using electronic databases and the resources of the Florida International University Research Library. Forty-two RCTs were selected for review, and their design and outcomes were compared and contrasted conceptually and in the form of tables.

Results: Most of the RCTs (n=31) were conducted before the advent of ART, and their aims were delaying disease progression, reversing malnutrition, and improving pregnancy outcomes in women and infants infected with HIV. The RCTs conducted with coadministration of ART were fewer (n=11), with relative smaller sample size, of shorter duration, and mainly focused on preventing or ameliorating the nutrition-related conditions generated by the chronic infection, its treatment, and the aging of PLWH.

Conclusion: As ART is becoming more accessible worldwide, and people are living longer with the disease, more longitudinal trials of nutritional interventions with larger sample sizes are needed to study the nutritional consequences and potential treatments for PLWH.

Keywords: HIV, antiretroviral therapy, micronutrients, probiotics, AIDS, randomization, clinical trial

Introduction

In limited-resource countries, severe malnutrition continues to be a growing problem, and it is frequently superimposed on the ongoing HIV pandemic.¹ Studies among people living with HIV (PLWH) have found metabolic and nutritional abnormalities, which may be either secondary to the HIV infection or due to primary malnutrition caused by insufficient intake. Nutritional deficiencies, when present, compromise the immune system and facilitate HIV disease progression.² In HIV disease, immunodeficiency and deficits in nutrition interact early in the disease, before antiretroviral treatment (ART) is provided; however, nutritional deficits and its possible consequences have also been observed after the disease is managed with ART.^{3,4} Antiretrovirals are life-saving medications that, although do not cure the disease, control its progression^{5,6} and improve

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nutritional status^{7,8} but generate new nutritional challenges. The nutritional problems observed in patients on ART differ from those seen prior to the provision of treatment;^{7,9–11} therefore, the purpose and formulation of the nutritional supplementation should also change. Different from previous reviews of nutritional supplementation in HIV infection, this review of randomized clinical trials (RCTs) of nutritional supplementation in PLWH for the first time considers the coadministration of ART and divides the review according to whether antiretrovirals were used in the trials.

ART suppresses the HIV virus and helps in the recuperation of the immune function. However, only about one-third of patients who achieve viral control recover protective immunity. Poor recovery of the immune function places these patients at increased risk of morbidity and mortality.^{12–14} Moreover, ART combinations containing some of the early antiretrovirals may increase oxidative stress, mitochondrial injury, and increase the host's needs for antioxidants.^{15–20} Chronic ART has also been associated with gastrointestinal (GI) symptoms that may decrease nutrient absorption and metabolism.²¹

Several reports suggest that micronutrient supplementation may support the immune system before and during the chronic use of ART^{22–25} and prevent ART-associated mitochondrial damage.^{26,27} Multivitamins and minerals are essential for supporting innate immunity, preventing its decline and promoting a timely reconstitution of the specific immune system.^{15–18,23,28} Most of the RCTs of nutritional supplementation reviewed by this work were performed before the availability of ART and demonstrated the immunostimulatory effects of micronutrients in PLWH (Table 1).

The trials in which nutritional supplements were coadministered with ART are few (Tables 2 and 3), with a limited sample size and duration of supplementation. The lack of emphasis on nutritional supplementation after the advent of ART might be due to expectations that treatment with antiretrovirals would have reversed nutritional and metabolic alterations. The interpretation of the findings of RCTs in which nutritional supplements were coadministered with ART is complex. ART combinations are multiple, and the selection of the combination for a given patient depends on the genetics of the host and virus, the degree of resistance to certain antiretrovirals, and personal and national socioeconomic conditions.

This review highlights the benefits of nutritional supplementation before ART is initiated and the scarcity of sufficiently powered RCTs that evaluate the impact of nutritional

supplementation during ART on immune recovery, morbidity, and mortality in PLWH.

Background

The literature indicates that nutritional deficiencies are widespread in PLWH, which are manifested early in the infection, before clinical symptoms are present, and prior to initiating ART.^{28–38} Although the use of ART has been shown to reduce wasting, the condition is still prevalent among patients receiving ART.¹⁰ In the era of ART, wasting is more frequently observed in cases with virologic and/or immunological failure, who are living in poor socioeconomic conditions and with high food insecurity.^{10,39} Micronutrient deficiencies have also been observed, even in patients receiving chronic ART. Jones et al⁴⁰ reported a high prevalence of zinc deficiency in participants on ART, adjusting for parameters of acute-phase reaction.

The continuous struggle of the immune system to control HIV may produce a hypermetabolic state, which is associated with increased caloric expenses, high rates of fat oxidation,⁴¹ and rapid depletion of essential micronutrients.²⁹ Therefore, adequate nutritional intake is critical for PLWH, particularly before initiation of ART, to offset the increased nutritional needs for calories and proteins produced by competition for these nutrients with the virus and the demands placed by a continuously activated immune system. The development of combined ART brought expectations that, once the virus was under control, the immune system would recover, the increased nutritional demands would diminish, and nutritional disturbances would be reversed.

Depletion of memory T-cells in the GI mucosa is the consequence of symptoms of diarrhea and malnutrition caused by HIV, which in turn causes bacterial translocation, which furthers immune activation, inflammation and oxidative stress, contributing to HIV progression.^{42–44} Other GI manifestations observed in the pre-ART era were chronic enteropathy and altered GI integrity.^{45,46}

ART, however, has also affected GI integrity; patients receiving ART have complications related to colitis associated with antimicrobial medications, side effects of ART,⁴⁷ and changes in microbiota.⁴⁸ Bacterial translocation produced by altered gut integrity has been linked with failure of immune recovery after initiation of ART.⁴⁹ Therefore, as it has been concluded for other conditions, it is important to consider strategies to improve GI integrity and reduce bacterial translocation by improving the composition of the microbiota through the optimization of probiotic supplementation.^{50–52}

Table 1 Randomized clinical trials of nutritional supplementation before initiation of ART

Authors (year)	Population	Formula	Outcomes
Sudfeld et al (2014) ⁸²	420 HIV+ pregnant women enrolled at 12–27-week gestation in Tanzania.	200 µg elemental Se (selenomethionine) All women received multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E and standard doses of antenatal folic acid and 120 mg ferrous iron.	Se supplementation increased the relative risk of HIV-1 RNA >50 copies/mL detection in breast milk (36% vs 27.5%) among primiparous but not multiparous women who were not receiving ART.
Baum et al (2013) ⁷⁹	878 HIV+ adults in Botswana.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E, in one arm, or multivitamins combined with 200 µg of elemental Se (selenomethionine) in the second arm, or 200 µg of Se alone in the third arm, or placebo in the fourth arm.	24-Month supplementation with a single supplement containing multivitamins and selenium was safe and reduced the risk of immune decline and morbidity when started in the early stages of HIV disease.
Mda et al (2013) ⁷⁹	201 children 4–24 months in South Africa.	300 µg retinol, 0.6 mg thiamin, 0.6 mg riboflavin, 8 mg niacin, 0.6 mg pyridoxine, 1 µg cobalamin, 70 µg folic acid, 25 mg ascorbic acid, 5 µg I,25-dihydrocholecalciferol, 7 mg D,L-tocopherol, 700 µg copper, 8 mg iron, 30 µg selenium, and 8 mg zinc.	Micronutrient supplementation significantly reduced episodes of diarrhea and respiratory symptoms, and improved malnutrition.
Arsenault et al (2010) ⁸⁴	674 HIV+ antiretroviral-naïve Tanzanian women.	1) vitamin A (1,500 µg RE of retinol) plus 30 mg β-carotene; 2) multivitamins (20 mg thiamin, 20 mg riboflavin, 25 mg vitamin B ₆ , 100 mg niacin, 50 µg vitamin B ₁₂ , 500 mg vitamin C [purified L-ascorbic acid], 30 mg vitamin E [RRR-α-tocopherol acetate], and 0.8 mg folic acid); 3) multivitamins with vitamin A plus β-carotene; or 4) placebo. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter.	Supplementation of HIV-infected women with vitamins increased the risk of subclinical mastitis.
Villamor et al (2010) ⁸⁵	594 Tanzanian HIV+ women.	1) vitamin A with β-carotene (VA/BC): 5,000 IU preformed vitamin A plus 30 mg β-carotene); 2) multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg vit B ₆ , 100 mg niacin, 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E; 3) multivitamins plus VA/BC; or 4) placebo.	Vitamin A with β-carotene supplementation in lactating women increases the HIV load in breast milk.
Kawai et al (2010) ⁸⁷	1,129 HIV-infected pregnant women in Tanzania.	Multivitamin supplements: (B complex: thiamin, riboflavin, niacin, B ₆ , B ₁₂ , and vitamins C and E) at a single dose of the RI compared to 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E. All women received standard doses of antenatal folic acid and 120 mg ferrous iron.	Supplementation of multivitamins at the recommended intake (RI) levels is as effective as multiple doses of the RI in decreasing risk of adverse pregnancy outcomes among HIV+ women.
Kupka et al (2009) ⁸⁸	915 HIV+ pregnant Tanzanian women.	All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Supplement: selenomethionine, 200 µg daily, compared to placebo. All women received: antenatal ferrous iron (60 mg/d), and 20 mg riboflavin, 110 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E.	Supplementation with Se during pregnancy and postpartum reduced diarrheal morbidity risk by 40% with no significant risk for anemia. No effect on morbidity end points.

(Continued)

Table 1 (Continued)

Authors (year)	Population	Formula	Outcomes
Webb et al (2009) ⁸³	626 HIV+ pregnant women in Tanzania.	Women were randomized into one of four formulas: 1. Vit A and β -carotene (VA + BC): 5,000 IU (1,500 μ g retinol equivalents) of preformed vit A plus 30 mg of β -carotene). 2. Multivitamins: 20 mg of thiamine, 20 mg of riboflavin, 25 mg of vit B ₆ , 100 mg of niacin, 50 μ g of vitamin B ₁₂ , 0.8 mg of folic acid, 500 mg of vit C, and 30 mg of vit E. 3. Multivitamins plus vit A. 4. Placebo. The two groups of women who receiving vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Supplement: selenomethionine, 200 μ g daily, compared to placebo. All women received: antenatal ferrous iron (60 mg/d), and 20 mg riboflavin, 110 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, and 200 μ g of Se, compared to placebo. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E, compared to placebo. Vitamin A: 30 mg β -carotene + 5,000 IU preformed vitamin A, compared to placebo. Combined multivitamins with vit A compared to placebo. The two groups of women receiving vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, compared to placebo. Vitamin A: 30 mg β -carotene + 5,000 IU preformed vitamin A, compared to placebo.	Sustained supplementation of HIV-infected breastfeeding mothers with this multivitamin formula is an effective intervention to improve vitamin E concentrations in breast milk. Although supplementation with vitamin A and β -carotene increased concentrations of breast milk retinol, it was not recommended in HIV+ mothers due to the elevated risk of vertical transmission.
Kupka et al (2008) ⁵⁹	913 HIV-infected pregnant women in Tanzania and their children.	Supplement: selenomethionine, 200 μ g daily, compared to placebo. All women received: antenatal ferrous iron (60 mg/d), and 20 mg riboflavin, 110 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, and 200 μ g of Se, compared to placebo.	Maternal supplementation with selenium during pregnancy and postpartum reduced risk of child mortality after 6 weeks of delivery.
Villamor et al (2008) ⁶⁰	471 HIV-positive and 416 HIV-negative adults with pulmonary TB in Tanzania.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, and 200 μ g of Se, compared to placebo.	Multivitamin supplementation with selenium increased CD3+ and CD4+ cell counts and decreased the incidence of extrapulmonary TB and genital ulcers in HIV-negative patients. Reduced the incidence of peripheral neuropathy by 57%, irrespective of HIV status.
Villamor et al (2007) ⁶¹	829 HIV+ pregnant and lactating women in Tanzania, and their infants up to 24 months of age.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E, compared to placebo. Vitamin A: 30 mg β -carotene + 5,000 IU preformed vitamin A, compared to placebo. Combined multivitamins with vit A compared to placebo. The two groups of women receiving vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, compared to placebo. Vitamin A: 30 mg β -carotene + 5,000 IU preformed vitamin A, compared to placebo.	Children born to the supplemented women in the three arms (including vitamin A) significantly decreased the burden of malaria. Also children supplemented with vitamin A after 6 months of delivery and up to 24 months of age had reduced risk of malaria.
Fawzi et al (2007) ⁶²	1,078 HIV+ pregnant women in Tanzania.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 μ g vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, compared to placebo. Vitamin A: 30 mg β -carotene + 5,000 IU preformed vitamin A, compared to placebo.	Multivitamin supplementation provided during pregnancy and in the postpartum period resulted in significant improvements in hematologic status among HIV-infected women and their children.

	Combined multivitamins with vit A compared to placebo. The two groups of women receiving vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E, compared to placebo. Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A, compared to placebo. Combined multivitamins with vit A compared to placebo. The two groups of women receiving vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron.		
Smith Fawzi et al (2007) ⁵³	1,078 HIV+ pregnant women.		Multivitamin supplementation reduced the risk of elevated depressive symptoms comparable to major depressive disorder and improvement in quality of life.
Villamor et al (2006) ⁷⁵	400 HIV-infected pregnant women in Tanzania.	Supplement: 25 mg of zinc or placebo. All women received daily: 20 mg thiamin, 20 mg riboflavin, 25 mg vit B ₆ , 100 mg niacin, 50 µg vit B ₁₂ , 500 mg vit C, 30 mg vit E, ferrous sulfate 60 mg, and 800 µg folate.	No effect on pregnancy outcomes, or maternal disease progression. Reduction in maternal midarm circumference. Potential for promoting anemia. Recommended not supplementing in HIV+ pregnant women.
Cárcamo et al (2006) ⁷⁶	159 HIV-infected adults with >7 days of diarrhea recruited at hospitals in Peru.	Supplement: 100 mg of elemental Zn compared to placebo.	Zn supplementation at this level had no significant effect on the duration or remission of diarrhea in HIV+ adults.
McGrath et al (2006) ⁶⁴	1,078 HIV+ pregnant women in Tanzania, and subset of 327 children born to these mothers.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E compared to placebo. Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo). Combined multivitamins with vit A compared to placebo. The two groups of women who received vit A also received a single dose of 200,000 IU of vit A at delivery. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin and mineral supplement: 5,000 IU vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg vit B ₆ , 40 mg niacin, 50 µg vit B ₁₂ , 0.8 mg folic acid, 200 mg vitamin C, 60 mg vitamin E, 200 IU vitamin D3, 200 µg Se, 5 mg copper, and 45 mg Zn, compared to placebo.	Maternal supplementation with multivitamins was protective against the risk for developmental delay on the motor scale in children from HIV+ mothers.
Range et al (2006) ⁶⁶	213 patients with TB + HIV, 286 patients with TB and HIV-negative.		Supplementation with multivitamins and minerals, including Zn, Cu, and Se during treatment of pulmonary TB reduced mortality in those coinfecting with HIV and TB.

(Continued)

Table 1 (Continued)

Authors (year)	Population	Formula	Outcomes
Bobat et al (2005) ⁶⁰	96 HIV+ children were randomized by age-group to receive Zn sulfate or placebo.	Supplement: 10 mg of elemental Zn as sulfate or placebo.	Children randomly assigned to Zn supplementation were less likely to get diarrhea than those on placebo ($P=0.001$). Supplementation did not have an adverse effect on viral load.
Villamor et al (2005) ⁶⁵	1,078 HIV+ pregnant women in Tanzania.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 0.8 mg folic acid, 500 mg vit C, 30 mg vit E compared to placebo. Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo). Combined multivitamins plus vit A compared to placebo.	Supplementation with multivitamins protected against wasting in HIV+ pregnant women.
Merchant et al (2005) ⁶⁹	1,078 HIV+ pregnant women in Tanzania.	All women received standard doses of antenatal folic acid and 120 mg ferrous iron. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 500 mg vit C, 30 mg vit E, and 0.8 mg folic acid (compared to placebo). Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo).	Women in the multivitamin supplementation groups reduced the risk for developing hypertension by 38% during pregnancy compared to those who were not on the multivitamins group.
Baylin et al (2005) ⁷⁰	716 HIV+ mother–infant pairs in Tanzania.	All women received standard doses of antenatal folic acid and 120 mg ferrous iron. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 500 mg vit C, 30 mg vit E, and 0.8 mg folic acid (compared to placebo). Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo). The two groups of women receiving vitamin A, also received a single dose of 200,000 IU of vitamin A at delivery.	Infants from supplemented mothers, including the vitamin A arms, compared to placebo, effectively improved the vitamin status of their children during the first 6 months of age, including retinol status.
Villamor et al (2005) ⁷¹	886 HIV+ mother and their infants in Tanzania.	All newborns received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter. Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 500 mg vit C, 30 mg vit E, and 0.8 mg folic acid (compared to placebo). Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo). The two groups of women receiving vitamin A, also received a single dose of 200,000 IU of vitamin A at delivery. All newborns received standard 200,000 IU or 100,000 IU if <1 year of age of vitamin A. All women received standard doses of antenatal folic acid and 120 mg ferrous iron.	Supplementation of HIV-infected women with multivitamins during pregnancy and lactation is an effective intervention for improving ponderal growth in their children.

Fawzi et al (2004) ²⁵	I,078 pregnant HIV+ women.	Supplementation with multivitamins delayed progression to WHO stage 4 ($P=0.02$), progression to stage 3 or higher ($P=0.003$). Multivitamins also resulted in significantly higher CD4+ and CD8+ cell counts and significantly lower viral loads.
McClelland et al (2004) ⁶⁸	400 HIV+ women in Kenya.	Supplementation resulted in higher CD4 and CD8 cell counts in the supplemented group, but increased participants' genital shedding.
Fawzi et al (2003) ⁷²	I,078 pregnant HIV+ women.	Supplementation with multivitamins prenatally and during breastfeeding seems to be protective of adverse pregnancy and child outcomes.
Jiamton et al (2003) ⁷⁴	481 HIV-infected men and women in Thailand with CD4 cell counts in the range of 50–550 cells/mm ³ .	Multiple micronutrient supplementation improved the survival of HIV-infected individuals with CD4 cell counts <200 cells/mm ³ .
Fawzi et al (2002) ⁸¹	I,078 pregnant HIV+ women.	Vitamin A supplementation increased mother-to-child transmission (RR =1.38, $P=0.009$) and had no effect on mortality after 24 months of supplementation. Multivitamin supplementation, however, reduced transmission risk in mothers with low CD4 cell count, low hemoglobin, and low-birth-weight newborns. Multivitamins also reduced mortality and increased survival in HIV-negative children born to malnourished HIV+ mothers with advanced disease.

(Continued)

Table 1 (Continued)

Authors (year)	Population	Formula	Outcomes
Villamor et al (2002) ⁸⁰	1,075 pregnant women.	Multivitamin supplement: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg vit B ₆ , 50 µg vit B ₁₂ , 500 mg vit C, 30 mg vit E, and 0.8 mg folic acid (compared to placebo). Vitamin A: 30 mg β-carotene + 5,000 IU preformed vitamin A (alone or with multivitamins compared to placebo). The two groups of women receiving vitamin A also received a single dose of 200,000 IU of vitamin A at delivery. All newborns received standard 200,000 IU or 100,000 IU if <1 year of age of vitamin A. All women received standard doses of antenatal folic acid and 120 mg ferrous iron. All newborns received: vit A at 100,000 IU at 6 months and 200,000 IU at the age of 1 year and every 6 months thereafter.	In pregnancy, supplementation with multivitamins, including multivitamins plus vitamin A, compared to placebo, and improved the rate of weight gain by 27% during the third trimester of pregnancy.
Kumwenda et al (2002) ⁹⁸	697 HIV+ pregnant women in Malawi.	The experimental group received 3 mg of retinol equivalent daily from the time of enrolment into the study to delivery. All women received standard 30 mg of elemental iron and 400 µg folate orally.	Vitamin A-supplemented pregnant women delivered higher birth-weight infants, and had fewer anemic infants at 6 weeks postpartum compared to placebo. Vitamin A supplementation did not affect mother-to-child perinatal HIV transmission.

Abbreviations: ART, antiretroviral treatment; HIV+, HIV positive; HAAT, highly active antiretroviral therapy; vit, vitamin; TB, tuberculosis; IU, international units; WHO, World Health Organization.

Nutritional interventions need to be individualized to the signs and conditions manifested by the patient, before or coadministered with ART, to preserve the innate immune response, support the recuperation of the immune system, and prevent comorbidities.²⁵

Micronutrient deficiencies associated with untreated HIV infection are vitamins A, C, E and D, B vitamins, and antioxidant minerals: selenium and zinc.^{29,33,34,53–55} Although a Cochrane review⁵⁶ found no definite evidence of the role of nutritional supplementation on morbidity, mortality, and HIV disease progression among PLWH, and vitamin A supplementation seems to be beneficial only in children, subsequent reports from RCTs of supplementation have found benefits for both adults and children.^{23–25,39,57–72} ART and nutritional supplementation are not in contradiction, as concluded by another review,⁷³ as each of them support the recovery of the immune system by different mechanisms.

This review focuses on evaluating RCTs of supplementation and their outcomes. Most of the RCTs reviewed had limitations, due to differences in length of supplementation, lack of measures of plasma levels of the supplemented micronutrients at baseline, diversity of the nutrients included in the formulas, and the variety in doses.

A number of RCTs reviewed also reported adverse unintentional outcomes of supplementation, such as the association of vitamin A supplementation with increased mother-to-child transmission,²⁵ iron with increased mortality,⁷⁴ selenium with vaginal HIV-shedding,⁶⁸ zinc with wasting in pregnant women receiving 25 mg of zinc,⁷⁵ and zinc in a dose of 100 mg elemental zinc/d with more frequency of diarrhea in patients with diarrheal condition.⁷⁶

Reports from RCTs that supplemented multivitamins with minerals demonstrated better outcomes than supplementation with a single nutrient.⁷⁷ Supplementation with multiple nutrients compared to a single nutrient on HIV disease outcomes suggests a synergistic interaction among nutrients (Tables 1 and 2), especially with nutritional antioxidants with a high level of metabolic interactions.⁷³ Because the efficacy of nutritional supplementation on HIV-disease parameters changes with the use of ART, the trials of supplementation were divided into two categories: trials in ART-naïve populations (Tables 1 and 3) and trials in which supplementation was coadministered with ART (Tables 2 and 3).

Some of the RCT formulas from the reviewed articles contained nonnutritional substances that were not directly

Table 2 Randomized clinical trials of supplementation among people living with HIV, who were receiving ART

Author (year)	Population	Design	Formula	Outcomes
Asdamongkol et al (2013) ⁹²	31 HIV+ patients with immunological discordance (controlled viral load, CD4 cell count <200 cells/ μ L).	RCT of supplementation for 6 months. Zn plasma levels were obtained at baseline.	Daily supplementation – 15 mg of chelated Zn compared to placebo.	The CD4+ cell count significantly increased ($P=0.042$) after zinc supplementation in patients with low plasma zinc levels at baseline ($N=12$).
Longenecker et al (2012) ⁸⁹	45 HIV+ adults in Cleveland (OH, USA) on ART and vit D deficiency.	Double-blinded RCT of supplementation for 12 weeks.	Vitamin D3 4,000 IU daily or placebo.	Improved vitamin D status and cholesterol but worsened insulin resistance without change in endothelial function.
Isanaka et al (2012) ⁸⁷	3,418 HIV+ initiating ART.	Double-blinded RCT of supplementation for 24 months.	Multivitamin supplements: low dose: 1.2 mg of thiamin, 1.2 mg of riboflavin, 15 mg of niacin, 1.3 mg of vit B ₆ , 2.4 μ g of vit B ₁₂ , 500 mg vit C, and 15 mg of vit E at a single dose of the RI compared to high dose: 20 mg of thiamin, 20 mg of riboflavin, 100 mg of niacin, 25 mg of B ₆ , 50 μ g of B ₁₂ , 0.8 mg folic acid, 500 mg vit C, and 30 mg vit E.	Receiving high-dose supplementation, compared to low dose, increased the relative risk of higher ALT levels by 44%, with no differential effect on disease progression. The study was stopped early.
Kakalia et al (2011) ⁹⁰	54 HIV+ children, 3–18 years old.	Nonblinded RCT of supplementation for 6 months.	One group received no supplementation, the second group received 5,600 IU/wk of vitamin D the third group received 11,200 IU/wk of vitamin D.	Vitamin D supplementation in doses of 11,200 IU/wk or higher does not impact CD4 count.
Baum et al (2010) ³⁹	231 HIV+ adults in Miami, FL, USA. 62.3% were on ART.	Double-blinded RCT of supplementation for 18 months.	Supplement: Zn gluconate (12 mg for females and 15 mg for males) compared to placebo.	Prevented immune failure (CD4 cell count <200 cells/ mm^3) and decreased diarrhea over time.
Arpadi et al (2009) ⁸⁸	56 HIV+ children and adolescents aged 6–16 years with serum 25-OHD ≥ 12 ng/mL, on ART.	RCT of supplementation for 12 months.	Supplement: vitamin D (100,000 IU/every 2 months) and calcium 1 g/d ($N=29$) or placebo daily ($N=27$).	Supplementation was safe, did not affect viral control or disease progression, and resulted in significant increases in serum vitamin D concentrations.
Hurwitz et al (2007) ⁸⁷	262 HIV+ adults in Miami. Mixed ART, 26.5% with no ART at baseline.	RCT of supplementation for 9 months.	Supplement: selenium yeast providing 200 μ g elemental selenium daily, compared to placebo.	Daily Se supplementation suppressed the increase of viral burden and provided indirect improvement in CD4 cell count.
Austin et al (2006) ⁸⁶	331 HIV+ patients in advanced disease (CD4 cell count ranged from 28 cells/ mm^3 to 114 cells/ mm^3) in Canada, and who were on combination protease inhibitor-based ART for at least 3 months.	Double-blinded RCT, multicenter (22 clinics). Supplementation for 13 months.	All participants received: β -carotene 30,000 IU (18 mg), 1,500 IU vit A, 56 IU vit D, 63 mg vit C, 56 IU vit E, 9.38 mg thiamin, 4.68 mg riboflavin, 2.25 mg riboflavin–50-phosphate sodium, 3.75 mg niacin, 9.38 mg niacinamide, 18.75 mg D-calcium pantothenate, 9.38 mg vit B ₆ , 3 mg vit B ₉ (pyridoxine-50-phosphate), 0.08 mg folic acid, 0.06 mg biotin, 9.38 mg choline bitartrate, 37.5 mg mg, 7.5 mg Zn, 1.5 mg Fe, 0.38 mg Cu, 1.5 mg mg, 9.38 mg K, 0.018 mg Cr, 0.018 mg Se, 0.00938 mg Mb, 0.00938 mg V, and 0.00938 mg I. Nonnutritional antioxidants: 150 mg N-acetyl-L-cysteine and 37.5 mg reduced glutathione.	Supplementation suppressed the increase of viral burden and provided indirect improvement in CD4 cell count. β -Carotene supplementation, in addition to the multivitamin/mineral/nonnutrient antioxidant formula, reduced mortality by more than three times (3.15 [1.10, 8.98], $P=0.03$) in those with advanced HIV disease after adjusting for baseline CD4 cell count and serum carotene.
			The treatment group also received: the formula above plus 72 mg of β -carotene/d.	

(Continued)

Table 2 (Continued)

Author (year)	Population	Design	Formula	Outcomes
Kaiser et al (2006) ²³	40 HIV+ patients.	Double-blinded RCT, comparing a formula to placebo. Supplementation for 12 weeks.	<p>Nonnutritional antioxidants: 1,200 mg N-acetyl cysteine, 100 mg acetyl-L-carnitine, and 400 mg α-lipoic acid.</p> <p>Vitamins: vit A 8,000 IU, β-carotene 20,000 IU, vit C 1,800 mg, 60 mg thiamin, 60 mg riboflavin, 60 mg pantothenic acid, 60 mg niacinamide, 60 mg inositol, 50 μg biotin, 260 mg vit B₆, 2.5 μg vit B₁₂, 400 IU vit D, 800 IU vit E, 300 mg bioflavonoids, 800 μg folate, and 60 mg choline.</p> <p>Minerals: 800 mg Ca, 18 mg Fe, 30 mg Zn, 400 mg mg, 200 μg Se, 150 μg I, 100 μg Cr, 10 mg Mn, 2.0 mg Cu, 300 μg Mb, 2.0 mg vit B, 99 mg K, and 150 mg betaine HCL.</p>	Nutritional supplementation in HIV+ patients on stable ART significantly increased CD4 cell counts after 12 weeks and experienced some reduction of neuropathy.

Abbreviations: ART, antiretroviral treatment; HIV+, HIV positive; RCT, randomized clinical trial; vit, vitamin; 25-OHD, 25-hydroxyvitamin D; RI, Recommended Intake; wk, week; Se, selenium supplementation; IU, international units; ALT, alanine aminotransferase.

addressed in this review and which are listed as nonnutrients in Tables 1 and 2. The observational research on these nonnutrient substances is scarce, and their evaluation is beyond the focus of this review.

Methods

This review followed the five steps of the Academy of Dietetics and Nutrition for conducting evidence-based review.⁷⁸ A systematic search of literature was conducted using PubMed and the resources of the Florida International University Library, including the Expanded Academic ASAP, Academic OneFile, Student Resources in Context, and Academic Search Complete to identify high-quality primary reports from RCTs of micronutrient and probiotic supplementation (Figure 1). The RCT design is considered to provide the strongest evidence.⁷⁸ The inclusion criteria for articles reviewed here were primary reports of RCTs in HIV-seropositive patients, ≥ 30 participants, published in the last 15 years, in English, and with and without coadministration of ART. Articles that did not meet the inclusion criteria were excluded after examination. The keywords used were HIV, nutrition, supplementation, RCT, micronutrients, vitamin, mineral, probiotic, and microbiota in different combinations to foster a wide number of results. The final selection included 42 reports of RCTs of nutritional supplementation in PLWH. These were divided into two categories: those conducted prior to the initiation of ART (n=31) and those in which nutritional supplementation was coadministered with ART (n=11).

The research questions that guided the review were

- Is nutritional supplementation beneficial in PLWH before and after the initiation of ART?
- How the objectives of the intervention differ before and after receiving ART?

Results

The majority of the formulas described in the reviewed reports (Tables 1–3) included several levels of B vitamins (thiamin, riboflavin, niacin, B₆, B₁₂, and folate)^{23,25,57–66,68–72,79–87} as these are important in the energy cycle of the mitochondria and for prevention of mitochondrial oxidative stress. Other antioxidant nutrients such as vitamins A, C, and E, selenium, and zinc were also included because the immune response to a chronic infection and some ART combinations may aggravate mitochondrial and systematic oxidative stress.^{15–19} Calcium and vitamin D were included in the formulas provided to cohorts that were coadministered ART^{23,88–90} because some

Table 3 Randomized clinical trials of probiotic supplementation

Authors (year)	Population	Design	Formula	Outcomes
In PLWH (pre-ART)				
Hummelen et al (2011) ¹⁰³	112 ART-naïve HIV patients in Tanzania	Randomized, double-blind, controlled trial of micronutrient and yogurt for 4 weeks	Micronutrient fortified yogurt with/without additional probiotic. Amount per 125 g of yogurt: <i>Lactobacillus rhamnosus</i> GR-1 at 10 ⁹ CFU/mL; vit A at 1,500 IU; vit E at 5.7 IU; niacinamide at 3.8 mg; thiamin at 0.3 mg; vit B ₁₂ at 0.6 µg; vit B ₆ at 0.3 mg; vit C at 21 mg; iron at 3.3 mg; selenium at 13.8 µg; zinc at 2.4 mg; DHA (omega-3) at 13 mg, and EPA (omega-3) at 19 mg	Micronutrient fortified yogurt was well tolerated by PLWH but not associated with a further increase in CD4 count after 4 weeks of supplement
Hummelen et al (2010) ¹⁰⁴	65 HIV+ women with aberrant microbiota in Tanzania (Nugent score 4–10)	Randomized, double-blind, placebo-controlled trial for 6 months	<i>L. rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14 supplementation compared to placebo	Supplementation of probiotic <i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 did not enhance the cure of bacterial vaginitis but significantly increased beneficial pH (OR =3.8, P=0.02)
In HIV population (post-ART)				
Van Niekerk et al (2014) ¹⁰⁵	74 HIV-exposed and 110 nonexposed premature (<34-week gestation) infants with a birth weight of ≥500 g and ≤1,250 g in Cape Town, South Africa	Randomized, double-blind, placebo-controlled trial supplemented for 28 days	Study group: breast milk plus a daily probiotic supplement of <i>L. rhamnosus</i> GG (0.35×10 ⁹ colony-forming units [CFU]) and <i>Bifidobacterium infantis</i> (0.35×10 ⁹ CFU); control group: breast milk plus a placebo consisting of medium-chain triacylglycerol (MCT) oil	Probiotics did not affect growth outcomes or incidence of feeding intolerance in HIV-exposure infants, but they had significantly higher Z-scores for length and head circumference than the unexposed newborns at the end of the study
Villar-García et al (2015) ¹⁰⁶	44 PLWH with controlled viral load <20 copies/mL	Double-blind, randomized, placebo-controlled trial	Oral supplementation with probiotics (<i>Saccharomyces boulardii</i>) or placebo for 12 weeks	<i>S. boulardii</i> treatment decreased microbial translocation (LBP) and inflammation (IL-6) in HIV-1-infected patients with long-term virologic suppression

Abbreviations: PLWH, people living with HIV; ART, antiretroviral treatment; vit, vitamin; HIV+, HIV positive; OR, odds ratio; LBP, lipopolysaccharide-binding protein; IL-6, interleukin 6; EPA, eicosapentaenoic omega-3 fatty acid; DHA, decosahexaenoic omega-3 fatty acid.

of the treatment combinations, and HIV itself, seem to expose PLWH to bone mass losses.^{91–96} These nutrients were supplemented either at the Recommended Dietary Allowance (RDA) levels⁹⁷ or at several times the RDA values. Summarizing the conclusions is difficult because of the various supplements provided in each trial and the lack of dose–response studies, but most outcomes of the studies that included these micronutrients showed that they were effective in delaying HIV disease progression and safe in ART-naïve populations (Table 1) and after ART initiation when given at nutritional doses (one RDA or under Tolerable Upper Intake Levels) (Table 2). Table 3 describes the trials that included probiotics in their formula.

RCTs of micronutrients in ART-naïve PLWH

Of the 29 RCTs reviewed in Table 1, 15 reports are from a longitudinal RCT of supplementation conducted in Tanzania, which included 1,078 HIV-infected, ART-naïve pregnant women who were followed for a median of 71 months. These pregnant women received 30 mg β-carotene + 5,000 IU preformed vitamin A alone, or a multivitamin with B vitamins and vitamins C and E alone, or a combination of both, or placebo in a 2×2 factorial design. In this trial, their newborns were followed for 18–24 months and supplemented with standard 100,000 IU of vitamin A at 6 months and 200,000 IU at 1 year of age and every 6 months thereafter.^{25,61–65,69–72,80,81,84,85}

The majority of the 15 articles reported benefits such as a reduction in the risk of vertical transmission with multivitamin supplementation, but not with vitamin A, in mothers with a low CD4 cell count, low hemoglobin and low-birth-weight newborns, and that multivitamin supplementation increased the survival of HIV-negative newborns of malnourished mothers with advanced HIV disease.⁸¹ Multivitamins alone or with vitamin A improved maternal weight gain during the third trimester of pregnancy.⁸⁰ Multivitamins during pregnancy and breastfeeding reduced adverse pregnancy and child outcomes,⁷² including improving newborns' ponderal weight⁷¹ and vitamin E status,⁸³ protecting infants against motor developmental delays,⁶⁴ reducing maternal wasting,⁶⁵ hypertension,⁶⁹ symptoms of depression, improving women's quality of life,⁶³ delaying HIV disease progression during pregnancy,²⁵ and improving hematological outcomes in both mothers and infants. Supplementation with vitamin A during pregnancy improved the vitamin A status of infants.⁷⁰ The three supplementation arms, including those with vitamin A, decreased the burden of malaria in this cohort.⁶¹ Other reports from this trial, however, also described adverse effects, such as increased vertical transmission and increased viral load

in breast milk with vitamin A supplementation, without reduction in mortality,^{81,83-85} and risk of developing sub-clinical mastitis with multivitamins.⁸⁴ In contrast, Kumwenda et al⁹⁸ randomized a cohort of 697 pregnant women in Malawi to receive 3 mg daily of retinol or placebo, in addition to the standard iron and folate supplementation during pregnancy, and concluded that supplementation during pregnancy and postpartum had beneficial effects on newborns' birth weight and prevention of anemia, without changing the rate of mother-to-child transmission.

Baum et al⁷⁹ supplemented 878 PLWH in Botswana with a multivitamin formula (a B complex with vitamins C and E based on that used by Fawzi et al²⁵) in a double-blinded RCT with a 2x2 factorial design. The participants were randomized to selenium (200 µg of elemental selenium) alone in the first arm of the study, or to multivitamins alone in the second arm, or multivitamins and selenium in combination in the third arm, compared to placebo. The participants were followed for 24 months, and the end points were CD4 cell count <250 cells/µL, AIDS-defining conditions, and combinations of both end points as a parameter of HIV disease progression. The supplementation of multivitamin and

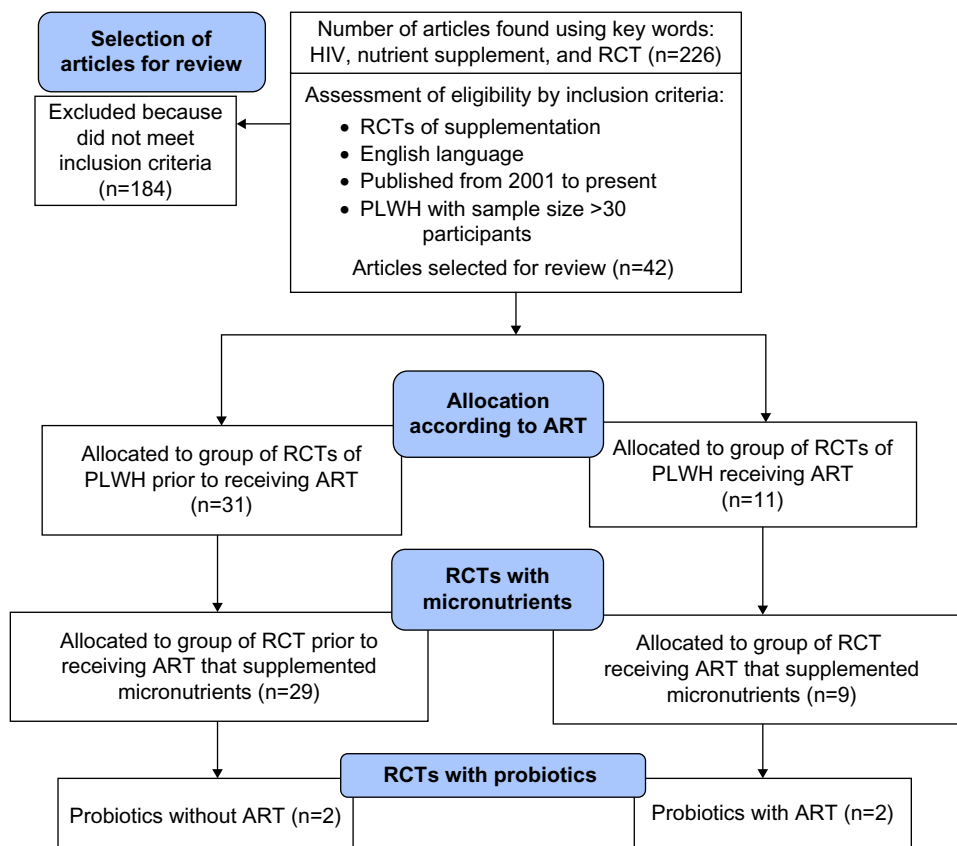


Figure 1 Consort flow diagram.

Abbreviations: RCT, randomized clinical trial; PLWH, people living with HIV; ART, antiretroviral treatment.

selenium was safe and reduced the risk of immune decline and morbidity (Table 1). These findings were consistent with those of Jiamton et al²⁴ who reported that supplementation with a complex formula with micronutrients and cysteine improved the survival of persons with advanced HIV disease (<200 cells/ μ L).

Sudfeld et al,⁸² using the multivitamin formula previously described by Fawzi et al²⁵ and Baum et al⁷⁹ (B complex with vitamins C and E), compared the multivitamin arm with an experimental arm with multivitamins plus 200 μ g of selenium, in a cohort of 420 pregnant women enrolled at 12–27-week gestation and followed until 6 months postpartum. The authors found that in primiparous women, but not in multiparous, the addition of selenium increased the relative risk of HIV-RNA shedding in breast milk.

In a cohort of 915 HIV-positive pregnant women, who were supplemented with multivitamins and selenium in a design similar to that of Sudfeld et al,⁸² Kupka et al⁵⁸ found that those who were supplemented with selenium had 40% fewer episodes of diarrhea without increased risk of anemia. In another report from this trial,⁵⁹ the investigators reported a reduced risk of mortality at 6 weeks after birth in children born to women supplemented with selenium and multivitamins. McClelland et al⁶⁸ also supplemented a similar formula to HIV-positive women in Kenya, and they found improvement in immune measures in those receiving the multivitamin with selenium formula (CD4 cell count + 23 cells/ μ L, $P=0.03$; and CD8 cell counts + 74 cells/ μ L, $P=0.005$) compared to placebo; however, they also reported an increase in HIV genital shedding among women receiving the formula.

The same formula of multivitamins with B vitamins and vitamin C and E^{25,79} was also combined with 25 mg of zinc, which is only slightly higher than the RDA recommendation (8 mg of zinc for women and 11 mg for men) and compared to placebo.⁷⁵ The experimental formula did not affect pregnancy outcomes or HIV disease progression. Villamor et al⁷⁵ also reported reduction in maternal midarm circumference, which suggested losses in fat or muscle mass in pregnant women receiving zinc with the multivitamin formula. Mda et al⁹⁹ randomized 201 children aged 4–24 months into a micronutrient formula appropriate for age or placebo for 6 months, and reported that those randomized into the micronutrient formula significantly reduced episodes of diarrhea, respiratory symptoms, and improved nutritional status.

Bobat et al¹⁰⁰ randomized 96 children with HIV disease to receive 10 mg of elemental zinc or placebo. The children who received the zinc dose were less likely to get diarrhea and did

not experience an increase in their viral load. In comparison, Cárcamo et al⁷⁶ supplemented 159 adults with HIV with a high dose of zinc (100 mg of elemental zinc) during episodes of diarrhea and did not find an effect on the duration or remission of diarrhea. The comparison of these two studies suggest that zinc supplementation, at lower doses and as prevention, is more effective than during episodes of diarrhea at a very high dose.

In an attempt to clarify the differential effects between high and nutritional doses of multivitamin supplementation, Kawai et al⁵⁷ compared a multivitamin formula that offered B vitamins and vitamins C and E at the Recommended Intake levels with the B vitamins and vitamins C and E used in higher doses in the aforementioned trials. No differences in adverse pregnancy outcomes were found between the two arms of the study.

In resource-limited countries, tuberculosis (TB) is a significant cause of mortality in PLWH without ART. PLWH who receive isoniazid medication, either as prevention or treatment of TB, may need supplementation with vitamin B₆. Receiving lower doses of isoniazid to prevent TB, or in high doses to treat it, may stir symptoms of neuropathy, because the medication blocks the absorption and metabolism of vitamin B₆. Supplementation with vitamin B₆ was found effective to prevent the symptoms of neuropathy associated with treatment.¹⁰¹ Villamor et al⁶⁰ conducted an RCT of multivitamins with B₆ and selenium compared to placebo among a cohort of 887 participants with pulmonary TB that included 471 HIV/TB-coinfected people. The authors reported a reduction in peripheral neuropathy by 57% in TB patients with and without HIV, which is consistent with Kaiser et al²³ (Table 2), who supplemented 40 PLWH receiving ART with a complex formula containing 260 mg of B₆ and reported improvement in neuropathy in patients on a stable ART combination associated with this condition.

RCTs of micronutrients in PLWH receiving ART

Two-thirds of the studies described in Table 2, after the initiation of ART, used single nutrients such as zinc, selenium, calcium, and vitamin D, which have been recognized to be deficient after initiation of ART.^{39,67,88,90,102} However, the articles led by Isanaka et al,⁸⁷ Austin et al,⁸⁶ and Kaiser et al²³ reported the use of multiple combinations of multivitamins.

Isanaka et al⁸⁷ compared a low dose to a high dose of the same formula of multivitamins supplemented to ART-naive patients in Africa^{25,79} and concluded that the high dose

increased liver transaminases without having a significantly different effect on HIV disease progression. Austin et al⁸⁶ compared a complex formula with multivitamins, minerals, and nonnutritional antioxidants with the same complex formula with an added higher dose of vitamin A and supplemented for 13 months. This was a multisite RCT in PLWH in advanced disease stage, receiving an ART combination containing protease inhibitors for at least 3 months. All participants received multivitamins and nonnutritional antioxidants as shown in Table 2. The investigators reported a reduced rate of mortality (odds ratio =3.15, $P=0.03$) in the group that received 120,000 IU (72 mg) of β -carotene compared to those who only received the standard formula, after controlling for serum carotene and CD4 cell count at baseline.⁸⁶

Kaiser et al²³ conducted a clinical trial of PLWH on stable ART using a complex formula with multivitamins, minerals, and nonnutritional antioxidants compared to placebo for 12 weeks. The investigators found that, compared to placebo, those who received the formula showed a significant increase in CD4 cell counts, with some reduction in neuropathy.

Two of the RCTs of supplementation addressed zinc deficiency in PLWH on ART. In a report from an RCT of zinc supplementation for 6 months, Asdamongkol et al¹⁰² randomized into zinc or placebo supplementation a group of 31 PLWH with immunological discordance (achieving controlled viral load without increasing CD4 cell count >200 cells/ μ L) and found that CD4 cell counts significantly increased in patients who started the study with low plasma levels of zinc. These findings agreed with those of a much larger study by Baum et al³⁹ of 231 adults living with HIV, who used illicit drugs, and were zinc deficient at randomization. The participants received either zinc at the level of 12 mg of elemental zinc for women or 15 mg for men or placebo for 18 months. Zinc supplementation prevented immune failure and decreased episodes of diarrhea.

As vitamin D deficiency has been identified as one of the side effects of long-term antiretroviral use, three of the reports of micronutrient supplementation after ART focused on vitamin D supplementation alone or with calcium.⁸⁸⁻⁹⁰ Arpadi et al⁸⁸ randomized 56 children living with HIV and receiving ART into 100,000 IU of vitamin D every 2 months and 1 g of calcium daily or placebo during 1 year; the investigators concluded that the intervention did not significantly affect viral control or HIV disease progression, but serum vitamin D significantly increased in those supplemented.

Longenecker et al⁸⁹ investigated the effects of supplementation with vitamin D on the endothelial function in PLWH. The study was an RCT that included 45 HIV patients

on ART therapy. Participants were randomized into the intervention group, which received 4,000 IU vitamin D₃, or into the placebo group and followed for 12 weeks. There was no difference in flow-mediated brachial artery dilation between the two groups ($P=0.748$). Serum vitamin D levels significantly increased in the intervention group ($P=0.003$) and total and non-HDL cholesterol were reduced. Interestingly, vitamin D supplementation was also associated with increased insulin resistance. Further investigation on this relationship is warranted.

Kakalia et al⁹⁰ also evaluated the effect of vitamin D supplementation on CD4 cell count in 54 children living with HIV, who were randomized into three groups: 800 IU of vitamin D/d, 1,600 IU of vitamin D/d, or no supplementation. Serum vitamin D levels significantly increased in the 800 IU/d ($P=0.0002$) and 1,600 IU/d ($P<0.001$) supplementation groups compared with control. Although vitamin D supplementation increased serum levels, CD4 cell count did not increase. The investigators also concluded that for maintaining adequate vitamin D levels in HIV-infected children, intakes of $\sim 1,600$ IU/d may be required. More longitudinal research is needed to identify potential risk factors for changes in bone mineral density in PLWH receiving specific ART combinations and develop effective medical and nutritional interventions.

RCTs of probiotic supplementation in PLWH

There have been very few trials of supplementation with probiotics before initiation^{103,104} or concomitant with ART^{105,106} in PLWH (Table 3). The majority of these trials were limited by small sample size, short duration of supplementation and one was combined with micronutrient supplementation.¹⁰⁵ Hummelen et al^{103,104} in two reports of RCTs conducted in ART-naive patients in Tanzania supplemented *Lactobacillus rhamnosus* GR-1. In the 2011 article, 112 participants received yogurt in combination with a multivitamin/mineral formula with omega-3 fatty acids, and the experimental group also received *L. rhamnosus* GR-1 at 10^9 CFU/mL. The investigators found that the fortified yogurt was well tolerated but did not significantly increase CD4 cell count. The main weakness of this study was that supplementation only occurred for 4 weeks, probably a very short time to observe long-term outcomes. A longer trial of supplementation of probiotics for 6 months by these investigators in Tanzania¹⁰⁶ found that supplementation with *L. rhamnosus* GR-1 and *L. reuteri* RC-14 did not seem to have an effect on bacterial vaginitis but changed the vaginal pH in a beneficial manner that may prevent the condition.

Discussion

A Cochrane review that combined the results from the trials of vitamin A supplementation among pregnant women living with HIV determined that supplementation with vitamin A did not reduce or prevent mother-to-child HIV-1 transmission.¹⁰⁷ However, other investigators have confirmed benefits in other pregnancy outcomes such as improved birth weight, and lower rates of infant morbidity and mortality.^{72,73} A review by Mehta and Fawzi,⁵⁵ which concurred with a 2005 Cochrane review,⁵⁷ reported that vitamin A supplementation should be recommended, because it was beneficial in reducing all-cause mortality and morbidity in infants and children infected with HIV. In adults, vitamin A supplementation in excess of the RDA is not recommended due to its adverse effects on mother-to-child transmission, increased HIV breast milk shedding and lack of effect on HIV disease progression.

The majority of studies in PLWH in Table 1, who were ART-naive, used formulas of multivitamins in factorial designs compared to single nutrients or to a combination of multivitamins plus the specific single nutrients or placebo. In contrast, most of the studies after the initiation of ART used single nutrients such as zinc, selenium, calcium and vitamin D, which have been recognized to be deficient after initiation of ART.^{39,67,88–90,102,105,106} The report from Isanaka et al⁸⁷ suggests that supplementation with multivitamin at the RDA level is still safe in coadministration with ART, but high doses of vitamins should be avoided.

Another study assessed the effect of vitamin supplements on HIV shedding in breast milk in HIV-infected lactating women. Tanzanian lactating women (n=594) were randomized into four groups: placebo, multivitamin, vitamin A and β -carotene, multivitamin with vitamin A plus β -carotene. They found that mothers taking vitamin A and β -carotene had higher detectable viral load than mothers not receiving vitamin A. They concluded that supplementing HIV-infected lactating mothers with vitamin A and β -carotene increases the HIV viral load in the breast milk and, therefore, increases the risk of mother-to-child transmission.⁸⁵

The benefit of using formulas that contain multiple nutrients is that vitamins and minerals work in conjunction with each other. Providing multiple micronutrients could influence several mechanisms simultaneously, and the effect, instead of being simply additive, becomes synergistic. One of the main limitations of these trials of multiple supplementation is that it is not possible to know which of the vitamins and minerals had more activity, which is important information to optimize formulas.

Recent studies suggest that microbial translocation is a source of immune activation even in PLWH with a

suppressed HIV viral load.^{108,109} Elevated plasma levels of endotoxins, which are lipopolysaccharides derived from the cell walls of gram-negative bacteria and a marker of microbial translocation, are produced due to a defective intestinal barrier and dysfunctional macrophage phagocytic clearance of microbial products.^{110,111} The microbial products trigger monocyte/macrophage activation that induces production of proinflammatory cytokines and soluble CD14 (sCD14).⁴² Depletion of CD4+ Th17 cells in the GI wall, early in HIV infection, reduces immunoprotection.^{112–115} The depletion also disrupts the microbiota of the patient, which may lead to greater dominance of potential pathogens, lower levels of lactobacillus species, and increases mucosal inflammation.¹¹⁶ Modulation of gut microflora has been suggested as a safe and promising treatment in HIV infection.^{117–119}

Probiotics have been shown to have favorable effects on alcoholic liver disease in clinical and experimental animal research.^{50–52,119} *L. rhamnosus Gorbach–Goldin* is one of the most widely studied probiotic strains with many well-documented benefits on several GI conditions and diseases.^{105,120} A limited number of studies using probiotic supplementation have been conducted in HIV infection;^{103–105,121–123} they have shown that probiotics were safe and effective in reducing diarrhea, nausea, and stabilizing CD4+ T-cell numbers.¹²⁴ *L. rhamnosus Gorbach–Goldin* also reduced the duration and severity of diarrhea and improved humoral immune responses.^{124,125} While most of these studies have been limited by a small number of study participants and/or short treatment duration,^{103–106} they support the notion that probiotics may provide benefits in HIV infection, especially among patients with chronic alcohol consumption.

Summary

In summary, the majority of the reviewed RCTs on nutritional supplementation in PLWH were conducted before ART was developed or initiated, underscoring the need for trials of nutritional supplementation that include PLWH who are receiving ART, to assist in the recuperation of the immune response, maintaining adequate immune activation, reduce inflammation, and reestablishing adequate microbiota, which may be impaired by the long-term exposure to HIV and its treatment.

The composition and doses of the formulas used prior and after ART were diverse, but there was a convergence of the investigators' judgment on using multivitamin formulas with a broader composition before ART was available or initiated. An essential objective of the nutritional supplementation of PLWH prior to their eligibility for ART was reversing

nutritional deficiencies that were identified in previous observational studies and delaying immune failure to prevent secondary infections.

After the advent and initiation of ART, the objectives of supplementation shifted to prevent the conditions that are associated with the chronic exposure to ART and associated with the aging of survivors, such as increased oxidative stress and increased morbidity for liver, kidney, cardiovascular disease, and cancers, all major causes of non-HIV-related deaths in PLWH.¹²⁶ Our review confirms that nutritional supplementation with micronutrients and probiotics is immune stimulatory in both RCTs with ART-naïve patients and in small trials with patients on ART and controlled viral load.

Conclusion

The main aim in the treatment of PLWH is preserving and enhancing the function of the immune system and reducing or controlling viral load. Immune reconstitution, however, does not always follow controlled viral load. While ART is provided according to prescribed standards to diminish HIV replication, the objectives of nutritional interventions in conjunction with ART should be achieving immune recovery, minimizing ART-related oxidative stress, preserving GI integrity, and preventing bacterial translocation and malnutrition. The literature, however, is sparse on research suggesting or demonstrating how to achieve these objectives through supplementation.

Currently, as the global effort to curtail the HIV epidemic is primarily directed toward broadening access to ART for PLWH in developing countries, and HIV is becoming a chronically managed disease in developed countries, research on HIV and nutrition should strive to evaluate the role of nutritional supplementation as a complementary therapy to ART. Further studies are needed to concentrate on the development of optimal nutrient formulas that foster immune recovery, decrease the short- and long-term nutritional adverse effects of ART, decrease bacterial translocation and immune activation, and prevent malnutrition. Trials with single nutrients may elucidate the role of the individual nutrients in achieving these objectives and support the incorporation of these nutrients into more complex formulas.

In PLWH, malnutrition inflicts an added immune-suppressive burden on the already immune-compromised system. Therefore, developing interventions for the prevention of nutrient deficiencies, with or without receiving ART, is still critical. Nutritional treatments should be individualized according to the patient's stage in the disease continuum, the type of ART combination used, the patient's nutritional

status such as undernutrition and obesity, environmental exposure to opportunistic infections, and specific socioeconomic surroundings.¹²⁷ Around the world, PLWH constitute clusters of very diverse populations, surrounded by different socioeconomic conditions that affect their access to treatment and their nutritional status. Recommendations for nutritional programs for PLWH need to be designed having in consideration this diversity.

Disclosure

The authors report no conflicts of interest in this work.

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